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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/656,270 | 09/05/2003 | Fritz Eckstein | 00-838-Q | 7134 |

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| EXAMINER |
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SHIN, DANA H

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| ART UNIT | PAPER NUMBER |
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1635

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| MAIL DATE | DELIVERY MODE |
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05/30/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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|------------------------------|------------------------|--|---------------------|--|
| Office Action Summary | Application No. | | Applicant(s) | |
| | 10/656,270 | | ECKSTEIN ET AL. | |
| | Examiner | | Art Unit | |
| | Dana Shin | | 1635 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5-16,20,21 and 24-26 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5-16,20,21 and 24-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☒ Certified copies of the priority documents have been received in Application No. 07/965,411.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>4-25-07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 23, 2007 has been entered.

Status of Claims

Claims 1-2, 5-16, 20-21, and 24-26 are pending and currently under examination on the merits.

Claim Objections

Claims 1 and 14 are objected to because of the following informalities: It appears that the claim language in last two lines contains typographical error because "2'-deoxy-2-fluoro" should be "2'-deoxy-2'-fluoro". Appropriate correction is required.

Claims 7-8 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of claim 1. Note that the 2'-deoxy-2'-fluoro modified nucleotides are limited to uridines and cytidines; that is, adenosine or guanosine nucleotides are not structural elements recited in claim 1. Applicant is required to cancel the

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claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 11, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The structure of the claimed ribozyme in claims 1 and 14 is unclear and internally inconsistent because as written, the claimed ribozyme is only required to comprise "at least one" modified nucleotide in lines 1-2 of claim 1 and lines 2-3 of claim 14. However, at the same time, the ribozyme is also required to have "at least two" modified nucleotides: at least one 2'-deoxy-2'-fluoro uridine and at least one 2'-deoxy-2'-fluoro cytidine. Since the metes and bounds of the claimed ribozyme structure is unclear and ambiguous, the claims are deemed indefinite.

Claim 11 recites the limitation "one or more said 2'-deoxy-2'-fluoronucleoitdes" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim, because claim 1 does not recite the word "2'-deoxy-2'-fluoronucleotides".

Claim 11 also recites the limitation "said oligoribonucleotide" in line 3. Since the word "oligoribonucleotide" is now deleted in claim 1, there is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 5-16, 20-21, and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sarver et al. (*Science*, 1990, 247:1222-1225) in view of Suzuki et al. (*Molecular Pharmacology*, 1987, 31:301-306) and Suhadolnik et al. (US 4,924,624).

The claims are drawn to a ribozyme of length between about 12 and about 36 nucleotides comprising either 2'-deoxy-2'-fluoro uridines or cytidines or both, at least one phosphorothioate linkage, wherein the modifications are placed at cleavage-sensitive locations, wherein the ribozyme further comprises a separate viral RNA that is HIV RNA.

Sarver et al. teach that hammerhead ribozymes consist of three stems and a catalytic center containing 13 conserved nucleotides and that the catalytic strand and the substrate strand can be on separate molecules (page 1222). They teach that ribozymes mediate cleavage of a substrate at 3' to the GUC, GUU, or GUA sequence (pages 1222-1223). They specifically teach a hammerhead ribozyme comprising HIV-1 *gag* RNA sequence as a separate substrate RNA strand. See Figure 2. They teach that one way to improve stability and cleaving activity of the ribozyme in an intracellular environment is the addition of a 5' cap structure (pages 1223-1224). Sarver et al. do not teach a ribozyme comprising at least one 2'-deoxy-2'-fluoro modified nucleotide and a phosphorothioate linkage.

Suzuki et al. teach that 2'-deoxy-2'-fluoro nucleoside analogues are stable to intracellular enzymes and that some nucleoside analogues have selective antiviral effect (pages 303-306). They teach that "future studies attempting to design nucleoside analogues which are stable to catabolic enzymes, but selectively utilized by HCMV metabolic enzymes" will be useful and favorable for therapeutic applications (page 306).

Suhadolnik et al. teach that phosphorothioate internucleotide linkages incorporated into oligonucleotide compounds increase metabolic stability and antiviral activity (columns 1-3). They further teach that a compound comprising phosphorothioate linkage groups inhibits HIV reverse transcriptase activity in cells (columns 33-35).

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It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the 2'-deoxy-2'-fluoro nucleoside analogues of Suzuki et al. and the phosphorothioate linkage groups of Suhadolnik et al. into the HIV-1 hammerhead ribozyme of Sarver et al.

One of ordinary skill in the art would have been motivated to combine the teachings of the prior art with a reasonable expectation of success, because the need to improve stability and cleaving activity of the ribozyme targeted to HIV-1 in an intracellular environment was recognized in the art as taught by Sarver et al. (pages 1223-1224) and because 2'-deoxy-2'-fluoro nucleoside analogues as well as phosphorothioate linkage groups were known to increase stability and antiviral effect of nucleic acids as taught by Suzuki et al. (pages 303-306) and Suhadolnik et al. (columns 33-35). That is, the ribozyme design method/technique of incorporating one or more 2'-deoxy-2'-fluoro-pyrimidines and a phosphorothioate linkage group to anti-HIV-1 ribozymes for improved stability and anti-viral effect in a cell was within the grasp of a person of ordinary skill in the relevant art at the time the instant invention was made. Further, since the exact cleavage sites of ribozymes are taught by Sarver et al. (pages 1223-1224), the skilled artisan would have been motivated to protect the cleavage sites from ribonuclease-mediated degradation by incorporating one or more 2'-deoxy-2'-fluoro-pyrimidines at the cleavage sites. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time the invention was made.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635


J. DOUGLAS SCHULTZ, PH.D.
SUPERVISORY PATENT EXAMINER